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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,391	10/28/2003	Jeffrey Isner	47624-CIP (71417)	6371

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/696,391	ISNER ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-52,54-65 and 68-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-52, 54-65, 68-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/16/09 has been entered.

Amended claims 49-52, 54-65, 68-70 are pending in the present application, and they are examined on the merits herein.

Priority

The present application is a continuation-in-part of U.S. Serial No. 09/265,071, filed on 3/9/1999, now issued US 6,676,937, which claims benefit of the provisional application 60/077,262, filed on 3/9/1998.

Upon review of the specifications of the U.S. Serial No. 09/265,071 and the provisional application 60/077,262 and comparison with the specification of the present application, it is determined that the examined claims are only entitled to the priority benefit of the filing date of 10/28/2003 for the following reasons. This is because there is no written support in either the parent U.S. application or in the provisional application for a method of inducing new blood vessel growth in myocardial tissue of a mammal in need of such treatment having at least the specific recited steps (a)-(c), and particularly comprising **the step of monitoring a cardiac function as recited in step (c)**; or **the**

step of administering to the treated mammal a broad genus of an anti-coagulant before, during, or after administration of the nucleic acid to the mammal (limitation of claim 61).

Accordingly, pending claims 49-52, 54-65 and 68-70 are only entitled to the priority date of 10/28/2003 for the reasons set forth above.

Should Applicants overcome the assigned priority date of 10/28/2003, claims 49-52, 54-65 and 68-70 are only entitled at best to the effective filing date of 3/9/1999 because the provisional application 60/077,262, filed on 3/9/1998 does not have a written support for a concept of co-administering a broad genus of an angiogenic factor or an effective fragment thereof to induce new blood vessel growth in the myocardial tissue of the mammal and ***increasing the frequency of EPC in the mammal****, particularly VEGF, SCF and any CSF, with an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Amended claims 49, 52, 54-56, 58-65 and 68-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner (WO 97/14307; Cited previously) in view of Hammond et al. (US Patent 5,880,090; IDS), Asahara et al. (Science 275:964-967, 1997; IDS) and Dillmann et al. (US 6,605,274; Cited previously). ***This is a modified rejection necessitated by Applicant's amendment.***

The instant claims are directed to a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such a treatment comprising: a) administering an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and b) administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, wherein the angiogenic factor or an effective fragment thereof is administered systemically, thereby inducing the new blood vessel growth in the myocardial tissue of the mammal, and increasing the frequency of endothelial progenitor cells in the mammal; and c) monitoring a cardiac function by echocardiography, ventricular end-diastolic dimension, end-systolic dimension, change in fractional shortening, wall motion score index, electromechanical mapping, cardiac angiography or LV systolic pressure, wherein the method improves said cardiac function.

Isner teaches a method for enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having cerebrovascular ischemia, renal ischemia, pulmonary ischemia, limb ischemia, ischemic cardiomyopathy and **myocardial ischemia** (page 4, lines 5-23). The method comprises the step of injecting to said

tissue with an effective amount of a nucleic acid capable of expressing an angiogenic protein by any injection means, and the nucleic acid may be carried by vehicles such as cationic liposomes, adenoviral vectors and that **nucleic acid encoding different angiogenic proteins may be used separately or simultaneously** (page 4, line 25 continues to line 8 of page 5). **Angiogenic proteins include aFGF, bFGF, VEGF (including VEGF165, see page 15, line 19), EGF, PDGF, PD-ECGF, HGF, colony stimulating factor (CSF), macrophage-CSF (M-CSF), granulocyte/macrophage CSF (GM-CSF) and nitric oxide synthase or muteins or portions thereof** (page 5, lines 10-22). Isner also teaches that the nucleic acid encoding an angiogenic protein is inserted into a cassette where it is operably linked to a promoter that is capable of driving expression of the protein in cells of the desired target tissue (page 9, line 28 continues to line 20 of page 10). **Isner further teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, while simultaneously inducing angiogenesis, including, for example, nitric oxide synthase, L-arginine, fibronectin, urokinase, plasminogen activator and heparin** (page 11, lines 15-19). Isner also discloses that catheters have been used for gene delivered in the art (page 1, line 23 continues to line 30 of page 2).

Isner does not teach specifically a further systemic administration of an effective amount of at least one angiogenic factor, specifically a stem cell factor (SCF), a colony stimulating factor (CSF) such as GM-CSF, G-CSF, or an effective fragment thereof into the mammal to induce new blood vessel growth **and to increase the frequency of**

endothelial progenitor cells. Isner also does not teach specifically to monitor a cardiac function by one of the recited approaches, even though Isner discloses monitoring collateral artery development in the medial thigh by angiography (page 21, lines10-25) or measuring calf blood pressure for physiologic assessment (page 22, liens 12-27).

At the filing date of the present application (10/28/03) Hammond et al already taught that cytokines such as stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient (see at least Summary of the invention). Hammond et al further note that **bone-marrow derived circulating CD34+ cells in the peripheral blood can participate in the repair of ischemic tissue** (col. 3, lines 28-37); and that the endothelialization-promoting agent can be administered by any route of delivery, including intravenously or subcutaneously which fall within the scope of a systemic administration as well as more than one endothelialization agent may be administered concomitantly (col. 4, lines 24-45).

Additionally, Asahara et al demonstrated clearly that circulating CD34+ cells from human peripheral blood can differentiate into endothelial cells *in vitro* and that *in vivo* these circulating endothelial progenitor cells home exclusively to and incorporate into sites of active angiogenesis in an ischemic tissue (see at least the abstract). Asahara et al further taught that EC progenitors may be useful for augmenting collateral vessel growth to ischemic tissues.

Dillmann et al already taught that clinical signs of improvement in cardiac performance and accommodation of stresses associated with congestive heart failure (CHF) are well known to those of ordinary skill in the cardiological art and may be determined, for example, by monitoring blood flow, cardiac pumping volume and ventricular pressure by for example, angiography and echocardiography, calcium transport rates, tolerance studies (col. 14, lines 14-26), as well as measurements of left ventricular end-diastole dimension (LVEDD), LV end-systolic dimension (LVESD), and fractional shortening (col. 25, line 37 continues to line 5 of col. 26).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of Isner by further administering systemically to the treated mammal an effective amount of at least one of SCF, GM-CSF, G-CSF, or an effective fragment thereof to induce new blood vessel growth and to increase the frequency of endothelial progenitor cells in the treated mammal in light of the teachings of Hammond et al and Asahara et al. Additionally, it would also have been obvious for an ordinary skilled artisan to monitor the cardiac function in the mammal treated for myocardial ischemia using any of the means recited in claim either 49 or claim 69 in light of the teachings of Dillmann et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because Hammond et al. already demonstrated that cytokines such as stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for

increasing endothelialization in a treated patient. Moreover, Asahara et al also demonstrated clearly that circulating CD34+ cells from human peripheral blood can differentiate into endothelial cells *in vitro* and that *in vivo* these circulating endothelial progenitor cells home exclusively to and incorporate into sites of active angiogenesis in an ischemic tissue and that the EC progenitors may be useful for augmenting collateral vessel growth to ischemic tissues. Therefore, this mobilization of endothelial cell progenitors would further enhancing blood vessel formation and growth in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the desired therapeutic outcome. Additionally, any of the means to monitor cardiac function taught by Dillmann et al is well-known and conventionally used by those of ordinary skill in the cardiological art to monitor clinical signs of improvement in cardiac performance, particularly for the treatment of ischemic cardiomyopathy and/or myocardial ischemia in this instance.

It is further noted that the monitoring means is not the patentable subject matter for the claimed methods because Applicants specifically state "cardiac function is monitored in the mammal by one or more combination of standard approaches to evaluate therapeutic outcome" (page 12, lines 24-25). The modified method resulting from the combined teachings of Isner, Hammond et al., and Dillman et al. is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Isner, Hammond et al., Asahara et al. and Dillman et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 50-51 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner (WO 97/14307; Cited previously) in view of Hammond et al. (US Patent 5,880,090; IDS), Asahara et al. (Science 275:964-967, 1997; IDS) and Dillmann et al. (US 6,605,274; Cited previously) as applied to claims 49, 52, 54-56, 58-65 and 68-69 above, and further in view of Asahara et al. (EMBO Journal 18:3964-3972, 1999). ***This is a modified rejection.***

The combined teachings of Isner, Hammond et al., Asahara (Science 275:964-967, 1997) and Dillmann et al. were presented above. However, none of the references teaches specifically a further administration to the mammal an effective amount of a VEGF or an effective fragment thereof to induce the new blood vessel growth in the myocardial tissue of the mammal and increasing the frequency of endothelial progenitor cells in the mammal.

However at the filing date of the present application (10/28/2003), Asahara et al (EMBO Journal 18:3964-3972, 1999) already demonstrated that recombinant human VEGF165 is capable of inducing mobilization of bone marrow-derived EPCs to augment neovascularization *in vivo* via intraperitoneal injection (a systemic administration) to complement its direct effect on fully differentiated endothelial cells (see at least the abstract and Materials and Methods).

Accordingly, it would have been obvious for an ordinary skilled artisan to further modify the method of Isner, Hammond et al, Asahara (Science 275:964-967, 1997) and Dillman et al. by also systemic administering to the treated mammal an effective amount of at least VEGF or an effective fragment thereof such as VEGF165 to induce new blood vessel growth and to increase the frequency of endothelial progenitor cells in the treated mammal in light of the teachings of Asahara et al (EMBO Journal 18:3964-3972, 1999).

An ordinary skilled artisan would have been motivated to carry out the above modifications because Asahara et al (EMBO Journal 18:3964-3972, 1999) already demonstrated that recombinant human VEGF165 is capable of inducing mobilization of bone marrow-derived EPCs to augment neovascularization *in vivo* via intraperitoneal injection to complement its direct effect on fully differentiated endothelial cells; and this mobilization of endothelial cell progenitors would further enhancing blood vessel formation in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the desired therapeutic outcome. The modified method resulting from the combined teachings of Isner, Hammond et al., Asahara (Science 275:964-967, 1997), Dillman et al., and Asahara et al. (EMBO Journal 18:3964-3972, 1999) is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Isner, Hammond et al., Asahara (Science 275:964-967, 1997), Dillman et al., and Asahara et al. (EMBO Journal 18:3964-3972, 1999), coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Amended claim 70 is rejected under 35 U.S.C. 103(a) as being unpatentable over Isner (WO 97/14307; Cited previously) in view of Hammond et al. (US Patent 5,880,090; IDS), Asahara (Science 275:964-967, 1997) and Dillmann et al. (US 6,605,274; Cited previously) as applied to claims 49, 52, 54-56, 58-65 and 68-69 above, and further in view of either Coleman (US 7,273,751) or Hu et al. (US 6,734,285) and with Pepper et al (J. Cellular Physiol. 177:439-452, 1998) and Bussolini et al. (J. Clin. Invest. 87:986-995, 1991; IDS). ***This is a modified rejection.***

The combined teachings of Isner, Hammond et al, Asahara et al. and Dillmann et al were already presented above. However, none of the references teaches specifically the use of an effective amount of a nucleic acid encoding VEGF-2 for inducing new blood vessel growth in myocardial tissue of a mammal in need, even thought Isner already taught a method for enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having cerebrovascular ischemia, renal ischemia, pulmonary ischemia, limb ischemia, ischemic cardiomyopathy and myocardial ischemia using an effective amount of a nucleic acid encoding a VEGF.

However at the filing date of the present application, both Coleman and Hu et al already taught separately that VEGF-2 is a potent angiogenic factor, and VEGF-2 polypeptide as well a nucleic acid molecule encoding VEGF-2 polypeptide are useful at least for treating various cardiovascular disorders, including myocardial ischemia,

congestive heart failure, congestive cardiomyopathy among others (see at least col. 45, line 13 continues to line 63 of col. 56 in US 7,273,751; col. 45, line 1 continues to line 31 of col. 56 in US 6,734,285).

Additionally, Pepper et al already demonstrated that VEGF-2 (VEGF-C) synergizes at least with either basic fibroblast growth factor (bFGF) or VEGF in the induction of angiogenesis in vitro (see at least the abstract and page 445, col. 2, second and third paragraphs).

Moreover, Bussolini et al also demonstrated that human recombinant G-CSF and GM-CSF are capable of inducing endothelial cells to proliferate and migrate *in vitro*, as well as repair of mechanically wounded endothelial monolayers, with an exemplification showing that recombinant G-CSF has also angiogenic activity *in vivo*. Additionally, recombinant G-CSF exhibits synergistic effects with bFGF in inducing *in vivo* angiogenesis (see at least abstract; Methods; Table IV; page 994, col. 1, first paragraph; col. 2, first full paragraph).

Accordingly, it would have been obvious for an ordinary skilled artisan to further modify the method of Isner, Hammond et al, Asahara et al. and Dillman et al. by also administering to the treated mammal an effective amount of a nucleic acid encoding VEGF-2 into the myocardial tissue as well as using at least combinations of angiogenic factors or proteins such as VEGF-2, G-CSF, VEGF and b-FGF to attain or maximize synergistic effects in inducing angiogenesis in light of the teachings of either Coleman or Hu et al together with Pepper et al. and Bussolini et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because both Coleman and Hu et al already taught separately that VEGF-2 is a potent angiogenic factor, and VEGF-2 polypeptide as well a nucleic acid molecule encoding VEGF-2 polypeptide are useful at least for treating various cardiovascular disorders, including myocardial ischemia, congestive heart failure, congestive cardiomyopathy among others. Additionally, Pepper et al already demonstrated that VEGF-2 (VEGF-C) synergizes at least with either basic fibroblast growth factor (bFGF) or VEGF in the induction of angiogenesis *in vitro*. Moreover, Bussolini et al. already demonstrated by exemplification that at least recombinant G-CSF has angiogenic activity *in vivo*, and that it also exhibits synergistic effects with at least another endothelial cell mitogen bFGF in inducing *in vivo* angiogenesis. The modified method resulting from the combined teachings of Isner, Hammond et al., Asahara et al., Dillman et al., and either Coleman or Hu et al. together with Pepper et al and Bussolini et al. is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Isner, Hammond et al., Asahara et al., Dillman et al., and either Coleman or Hu et al. together with Pepper et al and Bussolini et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejections in the Amendment filed on 3/16/09 (pages 6-18) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

1. Applicants argue basically that the primary Isner reference does not teach administration of an angiogenic factor (e.g.., GM-CSF, G-CSF, SCF), let alone systemic administration of such an angiogenic factor in currently amended claims. Applicants further argue that the primary Isner reference implicitly teaches away from systemic administration of angiogenic agents because of the underlying rationale for direct injection of tissue was to overcome the limitation of treatment methods in the prior art which required the repeated doses of angiogenic proteins by intramuscular administration over a range of 10 to 14 days; and that tissue injection also applies to combinations with other genes or their encoded gene products. Applicants further argue that the primary Isner reference does not teach methods for monitoring cardiac function.

Firstly, please note that the above rejection is made under 35 U.S.C. 103(a), and therefore the primary Isner reference does not have to teach every elements of the instant claims such as systemic administration of an angiogenic factor and/or means of monitoring cardiac function.

Secondly, there is no teaching away whatsoever by the primary Isner reference as argued by Applicants. The essential element of a method for inducing new blood vessel growth in myocardial tissue of a mammal in need thereof as set forth in the above rejection still **comprises or includes** the step of directly injecting into the

myocardial tissue an effective amount of a DNA sequence encoding an angiogenic protein to meet the limitation of step a) of the instant claims. **Nowhere in the Isner reference that teaches explicitly that encoded gene products (not in the form of a vector or DNA or RNA), such as the angiogenic protein nitric oxide synthase, must be administered directly to ischemic tissue and that they should not be administered systemically when they are used in combination with an angiogenic factor in the form of a plasmid or a viral vector or DNA to enhance the activity of targeted cells** (page 11, lines 11-19). It should be noted that an angiogenic factor in the form of a plasmid or a viral vector or DNA **must be directly administered to the target ischemic tissue in order to attain a desired therapeutic effect** due to the lack of in vivo vector targeting. However, **an angiogenic factor in the form of a protein and/or peptide is not necessarily required to be administered directly to the ischemic tissue in order to attain a desired therapeutic effect**. Isner states clearly "**Recent investigations have established the feasibility of using recombinant formulations of such angiogenic growth factors to expedite and/or augment collateral artery development in animal models of myocardial and hindlimb ischemia**" (page 8, first paragraph); and "**In addition, therapeutic angiogenesis has been achieved in the same or closely related models following administration of recombinant endothelial cell growth factor (ECGF) (Pu, et al., Circulation, 88:208-215 (1993)) and VEGF (Takeshita et al., Circulation, 90:228-234 (1994) supra). Previous studies, employing the animal model of chronic limb ischemia, demonstrated an efficacy of intra-muscular endothelial cell growth factor (ECGF)**

(Pu, et al., Circulation, 88:208-215 (1993)) or VEGF (Takeshita, et al., Circulation, 90:228-234 (1994) supra) administration" (page 8, second full paragraph). Additionally, in the prior art both Takeshita et al (J. Clin. Invest. 93:662-670, 1994; IDS) and Bauters et al. (J. Vasc. Surg 21:314-325, 1995) already demonstrated **therapeutic angiogenesis was achieved though a single-bolus systemic administration of VEGF; and Aharinejad et al (Bone 16:315-324, 1995; IDS) also demonstrated that subcutaneous injection treatment of CSF-1 or M-CSF promotes angiogenesis in the metaphysic of osteopetrotic rats**.

The cited statement in the primary Isner reference "In studies with recombinant angiogenic growth factors, intra-muscular administration of the growth factor was repeated over a range of 10 to 14 days. Thus, one major limitation of recombinant protein therapy is **its potential requirement** to maintain an optimally high and local concentration over time" (page 1, bottom of second paragraph) does not indicate or suggest in any shape or form that therapeutic angiogenesis would not be obtained via a systemic delivery of a recombinant angiogenic growth factor (see at least cited prior art in the above preceding paragraph). Furthermore, it is noted that Isner also teaches clearly that "If necessary, the nucleic acid may be reinjected to provide additional expression of the angiogenic protein" (page 5, lines 1-2). **This statement indicates clearly that the method of Isner also involves repeated doses or repeated injections to provide additional expression of an angiogenic protein**.

2. Applicants argue that there is no motivation to combine Isner and Hammond which teaches endothelialization of synthetic vascular grafts, and the citation of Asahara et al (Science 14:275:964-967, 1997) in Hammond does not amount to a specific teaching but a mere proposal concerning a possible role for CD34+ cells. Additionally, Applicants argue that there is nothing in Hammond that supports a role for EPCs in repairing ischemic tissue.

Isner teaches clearly that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells in a method for enhancing blood vessel formation or an angiogenesis in an ischemic tissue, including ischemic cardiomyopathy or myocardial ischemia, in a mammal. Hammond et al. teaches clearly that **SCF, GM-CSF, G-CSF are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for enhancing the endothelialization of synthetic vascular grafts in a patient. Hammond also notes that CD34+ circulating cells in blood can participate in the repair of ischemic tissue** (col. 3, lines 28-37). Furthermore, Asahara et al demonstrated clearly (**not simply a proposal**) that circulating **CD34+ cells from human peripheral blood can differentiate into endothelial cells *in vitro* and that *in vivo* these circulating endothelial progenitor cells home exclusively to and incorporate into sites of active angiogenesis in an ischemic tissue** (see at least the abstract). Asahara et al further taught that EC progenitors may be useful for augmenting collateral vessel growth to ischemic tissues.

As already pointed out in the above rejection, an ordinary skilled artisan would have been motivated to modify the method of Isner by further administering systemically to the treated mammal an effective amount of at least one of SCF, GM-CSF, G-CSF, or an effective fragment thereof to induce new blood vessel growth and to increase the frequency of endothelial progenitor cells in the treated mammal because Hammond et al. already demonstrated that cytokines such as stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient. Moreover, Asahara et al also demonstrated clearly that circulating CD34+ cells from human peripheral blood can differentiate into endothelial cells *in vitro* and that *in vivo* these circulating endothelial progenitor cells home exclusively to and incorporate into sites of active angiogenesis in an ischemic tissue and that the EC progenitors may be useful for augmenting collateral vessel growth to ischemic tissues. Therefore, this mobilization of endothelial cell progenitors would further enhancing blood vessel formation and growth in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the desired therapeutic outcome.

3. Applicants also argue that there is no motivation to combine Isner and Dillman and Dillman says nothing about improving cardiac function.

Once again, the above rejection is made under 35 U.S.C. 103(a), and therefore none of the cited references has to teach every limitation of the instant claims. It is

further noted that the above argument did not take into account of the overall teachings of Isner, Hammond et al., Asahara et al. and Dillman et al. as set forth in the above rejection. Moreover, any of the means to monitor cardiac function taught by Dillmann et al is well-known and conventionally used by those of ordinary skill in the cardiological art to monitor clinical signs of improvement in cardiac performance, particularly for the treatment of ischemic cardiomyopathy and/or myocardial ischemia in this instance. It is further noted that the monitoring means is not the patentable subject matter for the claimed methods because Applicants specifically state "cardiac function is monitored in the mammal by one or more combination of standard approaches to evaluate therapeutic outcome" (page 12, lines 24-25).

4. With respect to the secondary references of Asahara et al. (EMBO Journal 18:3964-3972, 1999), Coleman (US 7,273,751) and Hu et al (US 6,734,285), Applicants argue basically that none of these references teaches the combination of a nucleic acid encoding at least one angiogenic protein and at least one angiogenic factor, enhances the induction of blood vessel growth in a myocardial tissue.

Once again, the above rejection is made under 35 U.S.C. 103(a), and therefore none of the cited references has to teach every limitation of the instant claims. Please refer to the above rejections for motivations for the combined teachings of the cited references.

5. Applicants further argue that Applicants' disclosure demonstrates unexpected and surprising effective results as evidenced by examples 8-12, which showed that combo therapy resulted in superior improvement in all indexes of perfusion and function compared with all other treatment groups. Particularly, Applicants disclosed synergistic effect of cytokines (G-CSF+SCF) and VEGF-2 (gene transfer) in acute and chronic myocardial ischemia (MI) on page 58, lines 18-19 and data shown in Figures 8A-8E and 11A-11C. Applicants also argue that none of the cited references teaches or suggests that VEGF when administered with a cytokine would have a synergistic effect on cardiac function in ischemic myocardial tissues.

Firstly, the examiner acknowledged the synergistic effects of the specific combination of G-CSF (50 ng/g body weight) +SCF (200 ng/g body weight) and VEGF-2 (100 ug of plasmid vector VEGF-2) gene transfer in acute and chronic myocardial ischemia setting, in which both of the cytokines were administered subcutaneously daily for a week. However, it is noted that these specific reported "unexpected synergistic" effects are not reasonably extrapolated to a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such treatment as broadly claimed in any of the independent claims 49, 69 and 70. For example, at least the breadth of claim 70 does not necessarily limit to treating a mammal having acute and chronic myocardial ischemia; and/or G-CSF and SCF at any concentration can be administered at any other systemic administration routes. None of claims 49 and 69 requires the specific combination of G-CSF + SCF and VEGF-2 gene transfer.

Secondly, it should be noted **that the concept of using multiple growth factors to attain at least additional as well as synergistic effects (e.g., enhancing effects) for promoting cell proliferation and repair, including angiogenesis, is already established in the prior art** as evidenced at least by the teachings of Pepper et al, Bussolini et al cited in the above rejection and Ferrara et al. (US 5,322,671; IDS). For example, Pepper et al already demonstrated that **VEGF-2 (VEGF-C) synergizes at least with either basic fibroblast growth factor (bFGF) or VEGF** in the induction of angiogenesis in vitro (see at least the abstract and page 445, col. 2, second and third paragraphs). Moreover, Bussolini et al also demonstrated that recombinant **G-CSF has angiogenic activity *in vivo* and G-CSF also exhibits synergistic effects with bFGF** in inducing *in vivo* angiogenesis. Therefore, an ordinary skilled artisan would also reasonably expect that a combination comprising VEGF-2 and G-CSF would also yield synergistic effects on angiogenesis. Additionally, Ferrara et al also taught explicitly that VEGF can be combined with other novel or conventional therapies (e.g., growth factors such as aFGF, bFGF, PDGF, IGF, NGF, EGF, TGF-alpha) **for enhancing the activity of any of the growth factors including VEGF, in promoting cell proliferation and repair** (col. 16, lines 57-68). Therefore, the angiogenic effects contributed by the administration of an effective amount of a nucleic acid encoding at least one angiogenic protein (e.g., VEGF-2) or an effective fragment thereof are complemented or enhanced by the effects contributed by the administration of an effective amount of at least one angiogenic factor such as GM-CSF, G-CSF, SCF and VEGF or an effective fragment thereof due to their ability to mobilize bone-marrow derived endothelial progenitors that

can participate in the repair of ischemic tissues based at least on the teachings of Hammond et al., Asahara (Science 275:964-967, 1997), Asahara et al. (EMBO Journal 18:3964-3972, 1999), Pepper et al and Bussolini et al. as discussed above.

Thirdly, with respect to claim 70, it is further noted that the breadth of the claim encompasses additional use of angiogenic proteins/factors due to the language of the term "comprising". Additionally, the desired end-result of the method in claim 70 is simply improving a cardiac function in a treated mammal wherein said cardiac function is monitored by any of the means recited in claim 70. With respect to an untreated mammal, a mammal treated with an effective amount of a nucleic acid encoding VEGF-2 into the myocardial tissue alone (step a) would obviously have an improved cardiac function monitored by such recited means.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 49, 52, 54-56, 58-65 and 68-69 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 49-61, 63-66, 68-70, 72, 76-81 of copending Application No. 10/714,574 in view of Dillmann et al. (US 6,605,274; Cited previously). ***The rejection is modified.***

The instant claims are directed to a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such a treatment comprising: a) administering an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and b) administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, wherein the angiogenic factor or an effective fragment thereof is administered systemically, thereby inducing the new blood vessel growth in the myocardial tissue of the mammal, and increasing the frequency of endothelial progenitor cells in the mammal; and c) monitoring a cardiac function by echocardiography, ventricular end-diastolic dimension, end-systolic dimension, fractional shortening, wall motion score index, electromechanical mapping with a NOGA system, cardiac angiography or LV systolic pressure, wherein the method improves said cardiac function.

Claims 49-61, 63-66, 68-70, 72 and 76-81 of copending Application No. 10/714,574 are drawn to a method for treating ischemic myocardial tissue of a mammal in need of such a treatment comprising: a) identifying a mammal which has, is

suspected of having, or will have the ischemic tissue; b) injecting an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and c) administering to the mammal an effective amount of GM-CSF or a cytokine or an effective fragment thereof, thereby treating ischemic myocardial tissue of the mammal, wherein the GM-CSF or an effective fragment thereof is administered systemically.

The claims of the present application differ from the claims of the copending Application No. 10/714,574 in reciting the additional step of monitoring a cardiac function by any one of the approaches recited in the Markush group of anyone of claims 49 and 69.

At the filing date of the present application, Dillmann et al already taught that clinical signs of improvement in cardiac performance and accommodation of stresses associated with congestive heart failure (CHF) are well known to those of ordinary skill in the cardiological art and may be determined, for example, by monitoring blood flow, cardiac pumping volume and ventricular pressure by for example, angiography and echocardiography, calcium transport rates, tolerance studies (col. 14, lines 14-26), as well as measurements of left ventricular end-diastole dimension (LVEDD), LV end-systolic dimension (LVESD), and fractional shortening (col. 25, line 37 continues to line 5 of col. 26).

Accordingly, it would have been obvious for an ordinary skilled artisan at the time the invention was made to modify the method of the copending Application No. 10/714,574 by further monitor the cardiac function in the mammal treated for myocardial

ischemia using any of the means recited in anyone of claims 49 and 69 in light of the teachings of Dillmann et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because any of the means to monitor cardiac function taught by Dillmann et al is well-known and conventionally used by those of ordinary skill in the cardiological art to monitor clinical signs of improvement in cardiac performance, particularly for the treatment of ischemic cardiomyopathy and/or myocardial ischemia in this instance.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of the copending Application No. 10/714,574 and Dillmann et al., coupled with a high level of skill of an ordinary artisan in the relevant art.

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 70 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 51 of copending Application No. 10/714,574 in view of Dillmann et al. (US 6,605,274; Cited previously) as applied to claims 49, 52, 54-56, 58-65 and 68-69 above, and further in view of Hammond et al. (US Patent 5,880,090; IDS), Asahara et al. (Science 275:964-967, 1997; IDS), Pepper

et al (J. Cellular Physiol. 177:439-452, 1998) and Bussolini et al. (J. Clin. Invest. 87:986-995, 1991; IDS). ***This is a new ground of rejection.***

Claim 70 of the present application differ from claim 51 of the copending Application No. 10/714,574 in reciting administering an effective amount of G-CSF and SCF to induce new blood vessel growth in the myocardial tissue of the treated mammal and increasing the frequency of EPC in the mammal.

However, Hammond et al already taught that cytokines such as stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient (see at least Summary of the invention). Hammond et al further note that **bone-marrow derived circulating CD34+ cells in the peripheral blood can participate in the repair of ischemic tissue** (col. 3, lines 28-37); and that the endothelialization-promoting agent can be administered by any route of delivery, including intravenously or subcutaneously which fall within the scope of a systemic administration as well as more than one endothelialization agent may be administered concomitantly (col. 4, lines 24-45).

Asahara et al already demonstrated clearly that circulating CD34+ cells from human peripheral blood can differentiate into endothelial cells *in vitro* and that *in vivo* these circulating endothelial progenitor cells home exclusively to and incorporate into sites of active angiogenesis in an ischemic tissue (see at least the abstract). Asahara et

al further taught that EC progenitors may be useful for augmenting collateral vessel growth to ischemic tissues.

Additionally, Pepper et al already demonstrated that VEGF-2 (VEGF-C) synergizes at least with either basic fibroblast growth factor (bFGF) or VEGF in the induction of angiogenesis in vitro (see at least the abstract and page 445, col. 2, second and third paragraphs).

Moreover, Bussolini et al also demonstrated that human recombinant G-CSF and GM-CSF are capable of inducing endothelial cells to proliferate and migrate *in vitro*, as well as repair of mechanically wounded endothelial monolayers, with an exemplification showing that recombinant G-CSF has also angiogenic activity *in vivo*. Additionally, recombinant G-CSF exhibits synergistic effects with bFGF in inducing *in vivo* angiogenesis (see at least abstract; Methods; Table IV; page 994, col. 1, first paragraph; col. 2, first full paragraph).

Accordingly, it would have been obvious for an ordinary skilled artisan at the time the invention was made to further modify the method of the copending Application No. 10/714,574 and Dillman et al. by also systemic administering G-CSF and SCF to induce new blood vessel growth in the myocardial tissue of a treated mammal and increasing the frequency of EPC in the treated mammal, particularly using a nucleic acid encoding VEGF-2, in light of the teachings of Hammond et al, Asahara et al, Pepper et al and Bussolini et al. as discussed above.

An ordinary skilled artisan would have been motivated to further carry out the above modification because Hammond et al. already demonstrated that cytokines such

as stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient. Moreover, Asahara et al also demonstrated clearly that circulating CD34+ cells from human peripheral blood can differentiate into endothelial cells *in vitro* and that *in vivo* these circulating endothelial progenitor cells home exclusively to and incorporate into sites of active angiogenesis in an ischemic tissue and that the EC progenitors may be useful for augmenting collateral vessel growth to ischemic tissues. Therefore, this mobilization of endothelial cell progenitors would further enhancing blood vessel formation and growth in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the desired therapeutic outcome. Furthermore, Pepper et al already demonstrated that VEGF-2 (VEGF-C) synergizes at least with either basic fibroblast growth factor (bFGF) or VEGF in the induction of angiogenesis, while Bussolini et al. also demonstrated that at least recombinant G-CSF has angiogenic activity *in vivo* and exhibits synergistic effects with at least another endothelial cell mitogen bFGF in inducing *in vivo* angiogenesis.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of the copending Application No. 10/714,574, Dillmann et al, Hammond et al, Asahara et al., Pepper et al and Bussolini et al., coupled with a high level of skill of an ordinary artisan in the relevant art.

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 49-51 and 57 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 69 of copending Application No. 10/714,574 in view of Dillmann et al. (US 6,605,274; Cited previously) and Asahara et al. (EMBO Journal 18:3964-3972, 1999). ***This is a modified rejection.***

The instant claims are directed to a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such a treatment comprising: a) administering an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and b) administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, wherein the angiogenic factor or an effective fragment thereof is administered systemically, thereby inducing the new blood vessel growth in the myocardial tissue of the mammal, and increasing the frequency of endothelial progenitor cells in the mammal; and c) monitoring a cardiac function by echocardiography, ventricular end-diastolic dimension, end-systolic dimension, fractional shortening, wall motion score index, electromechanical mapping with a NOGA system, cardiac angiography or LV systolic pressure, wherein the method improves said

cardiac function, and wherein the angiogenic factor is a VEGF or an effective fragment thereof.

Claim 69 of copending Application No. 10/714,574 is drawn to a method for treating ischemic myocardial tissue of a mammal in need of such a treatment comprising: a) administering to a mammal an effective amount of a cytokine that mobilizes endothelial progenitor cells, wherein the cytokine or an effective fragment thereof is administered systemically; and b) subsequently administering an effective amount of a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue, wherein the method increases the neovascularization of said tissue thereby treating ischemic myocardial tissue of the mammal.

The claims of the present application differ from the claims of the copending Application No. 10/714,574 in reciting the additional step of monitoring a cardiac function by any one of the approaches recited in the Markush group of claim 49, and the angiogenic factor is VEGF or an effective fragment thereof.

At the filing date of the present application, Asahara et al already demonstrated that recombinant human VEGF165 is capable of inducing mobilization of bone marrow-derived EPCs to augment neovascularization *in vivo* by intraperitoneal injection to complement its direct effect on fully differentiated endothelial cells (see at least the abstract).

Additionally, Dillmann et al already taught that clinical signs of improvement in cardiac performance and accommodation of stresses associated with congestive heart

failure (CHF) are well known to those of ordinary skill in the cardiological art and may be determined, for example, by monitoring blood flow, cardiac pumping volume and ventricular pressure by for example, angiography and echocardiography, calcium transport rates, tolerance studies (col. 14, lines 14-26), as well as measurements of left ventricular end-diastole dimension (LVEDD), LV end-systolic dimension (LVESD), and fractional shortening (col. 25, line 37 continues to line 5 of col. 26).

Accordingly, it would have been obvious for an ordinary skilled artisan at the time the invention was made to modify the method of the copending Application No. 10/714,574 by further monitor the cardiac function in the mammal treated for myocardial ischemia using any of the means recited in claim 67 in light of the teachings of Dillmann et al., as well as further administering to the treated mammal an effective amount of at least VEGF or an effective fragment thereof such as VEGF165 to induce new blood vessel growth and to increase the frequency of endothelial progenitor cells in the treated mammal in light of the teachings of Asahara et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because any of the means to monitor cardiac function taught by Dillmann et al is well-known and conventionally used by those of ordinary skill in the cardiological art to monitor clinical signs of improvement in cardiac performance, particularly for the treatment of ischemic cardiomyopathy and/or myocardial ischemia in this instance. Furthermore, Asahara et al already demonstrated that recombinant human VEGF165 is capable of inducing mobilization of bone marrow-derived EPCs to augment neovascularization *in vivo* to complement its direct effect on fully differentiated

endothelial cells; and this mobilization of endothelial cell progenitors would further enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the desired therapeutic outcome.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of the copending Application No. 10/714,574, Dillmann et al., and Asahara et al., coupled with a high level of skill of an ordinary artisan in the relevant art.

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

This is a provisional obviousness-type double patenting rejection.

It is noted that the above provisional obviousness-type double patent rejections are not the only rejections in the instant application.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

1. Donahue et al. (Blood 87:1644-1653, 1996) demonstrated that G-CSF and/or SCF mobilized CD34+ cells from bone marrow to peripheral blood *in vivo* through subcutaneous injection (see at least the abstract).

2. Siena et al (Blood 74:1905-1914, 1989) demonstrated enhancement of circulating CD34+ hematopoietic stem cells in the peripheral blood of high-dose

cyclophophamide-treated patients by intravenous infusion of recombinant human GM-CSF (see at least the abstract).

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN/
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